Dysregulated follicular regulatory T cells and antibody responses exacerbate experimental autoimmune encephalomyelitis

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1. **簡述論文的概要以及重大發現：**

多發性硬化症(MS)是一種發生在中樞神經系統 (CNS)的自體免疫性疾病。造成疾病的主因，是由於人體自身的免疫系統攻擊及破壞神經髓鞘所導致。T_{FR} 的功能為抑制過度的 T_{FH} 和 GC B cell 增殖，T_{FH} 則是提供信號給 GC B 細胞，使 GC B 細胞分化為釋放抗體的細胞和記憶 B cell，T_{FR} 細胞透過抑制 T_{FH} 細胞的活化進而去抑制抗體(Ab)的產生。繼發於功能失調的 T_{FR} 細胞所導致 T_{FH} 細胞-GC-抗體 (Ab) 反應的失調會導致一系列自體免疫性疾病，本篇以 MS 為研究對象。本研究發現 Blimp1 對於維持 T_{FR} 細胞和抗體反應至關重要，且失調的 T_{FR} 細胞和抗體反應會促進中樞神經系統的自體免疫疾病。

2. **對論文內容的提問：**

Blimp1 缺陷的 Tregs 可能會進一步增強 CNS 發炎。但目前仍不知道究竟是 Tregs 和 T_{FR} 細胞中哪些訊號發生改變，進而導致 Blimp1 表達降低、穩定

性受損以及在 EAE 的抑制活性。

3. **論文的缺點與評論：**

在過去對於 MS 的研究中通常是著重於 Th1 及 Th17 細胞。儘管在近期的其他研究指出了 T_{FH}-B-GC 的反應對 EAE 和 MS 具有重要貢獻，但 T_{FH}-B 細胞以及抗體在 EAE 和 MS 調節中的反應仍然不清楚。本篇研究首次表明了 $Blimp1^{+}T_{FR}$ 細胞在 EAE 調節功能中的潛在作用，並發現 Blimp1 缺陷的 Tregs 及 T_{FR} 細胞，會轉化為產生 IL-17A/GM-CSF 的 Teff 細胞（稱為 exTregs），並導致周邊和中樞神經系統中異常 T_{FH} 增生和抗體產生增加。

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Abstract

Background: Follicular regulatory T (T_{FR}) cells are essential for the regulation of germinal center (GC) response and humoral self-tolerance. Dysregulated follicular helper T (T_{FH}) cell-GC-antibody (Ab) response secondary to dysfunctional T_{FR} cells is the root of an array of autoimmune disorders. The contribution of T_{FR} cells to the pathogenesis of multiple sclerosis (MS) and murine experimental autoimmune encephalomyelitis (EAE) remains largely unclear.

Methods: To determine the impact of dysregulated regulatory T cells (Tregs), T_{FR} cells, and Ab responses on EAE, we compared the MOG-induced EAE in mice with a FoxP3-specific ablation of the transcription factor Blimp1 to control mice. In vitro co-culture assays were used to understand how Tregs and Ab regulate the activity of microglia and central nervous system (CNS)-infiltrating myeloid cells.

Results: Mice with a FoxP3-specific deletion of Blimp1 developed severe EAE and failed to recover compared to control mice, reflecting conversion of Tregs into interleukin (IL)-17A/granulocyte-macrophage colony-stimulating factor (GM-CSF)-producing effector T cells associated with increased T_{FH}-Ab responses, more IgE deposition in the CNS, and inability to regulate CNS $CD11b^+$ myeloid cells. Notably, serum IgE titers were positively correlated with EAE scores, and culture of CNS $CD11b^+$ cells with sera from these EAE mice enhanced their activation, while transfer of Blimp1-deficient T_{FR} cells promoted Ab production, activation of CNS $CD11b^+$ cells, and EAE.

Conclusions: Blimp1 is essential for the maintenance of T_{FR} cells and Ab responses in EAE. Dysregulated T_{FR} cells and Ab responses promote CNS autoimmunity.

Keywords: CNS autoimmunity, Experimental autoimmune encephalomyelitis, Multiple sclerosis, Humoral antibody response, Follicular regulatory T cells, Treg lineage stability

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